UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/044,303	01/11/2002	Dietmar J. Manstein	1974.006	6803

7590 02/25/2003

Candice J. Clement, Esq.
HESLIN ROTHENBERG FARLEY & MESITI, P.C.
5 Columbia Circle
Albany, NY 12203

EXAMINER
STEADMAN, DAVID J

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 02/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/044,303	MANSTEIN ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *14-27 and 29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Application Status

[1] Claims 1-29 are pending in the application.

[2] Applicants' election without traverse of Group I, claims 1-13 and 28, in Paper No. 11, filed 12/09/02, is acknowledged.

[3] Claims 14-27 and 29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Oath/Declaration

[4] The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02. The oath or declaration is defective because: alterations which have not been initialed and/or dated as is required by 37 CFR 1.52(c). A properly executed oath or declaration which complies with 37 CFR 1.67(a) and identifies the application by application number and filing date is required.

Claim Objections

[5] Claim 6 is objected to because of the following informalities: the term "analog, fragment derivative thereof" is grammatically incorrect and should be replaced with, for example, "analog, fragment or derivative thereof". Appropriate correction is required.

[6] Claim 11 is objected to in the recitation of "SEQ ID NO. 1". The proper sequence identifier "SEQ ID NO:1" should be used instead. Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

[7] Claims 10 and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 10 is indefinite in the recitation of "immunologically relevant receptor". It is unclear as to how a skilled artisan determines the relevance of a receptor. Thus, the intended scope of immunologically relevant receptors is unclear.

b. Claim 12 is confusing as the claim recites "wherein (c)", however, neither of the claims from which claim 12 depends recites a part (c). It is suggested that applicants clarify the meaning of the claim. For examination purposes, the examiner has interpreted the claim as depending from claim 8.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[8] Claims 1-10, 12, 13, and 28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1 (claims 2, 3, 8, and 12 dependent therefrom), 4-7, 9, and 10 are drawn to a genus of recombinant proteins comprising (a) a first protein or an analog, fragment, or derivative thereof and (b) a target protein of interest (claim 1), and optionally wherein (b) is any amino acid sequence of at least 20 amino acids (claim 4); (a) comprises a sequence of a member of the myosin or kinesin superfamilies or

an analog, fragment, or derivative thereof and a target protein of interest (claim 5); (a) is selected from a myosin or kinesin families or an analog, fragment, or derivative thereof and a target protein of interest as recited in claim 6; (a) is a motor domain of a myosin or kinesin superfamily or an analog, fragment, or derivative thereof and a target protein of interest (claim 7); (b) is selected from the proteins as recited in claim 9; or (b) is selected from the proteins as recited in claim 10. The claims are rejected because the disclosure does not adequately describe a representative number of species of the genus of recombinant proteins that are encompassed by the claims. The specification describes only two representative species of the claimed genus, i.e., a recombinant fusion protein comprising myosin and a target protein of interest or a recombinant fusion protein comprising kinesin and a target protein of interest. A "representative number of species" means that the species that are adequately described are representative of the *entire* genus. While a description of a representative number of species does not require disclosure of individual support for all species within a claim, the disclosed species should nonetheless be representative of the claimed genus. The examiner acknowledges that the structures and corresponding functions of recombinant proteins, particularly fusion proteins, are well known to one of skill in the art. Furthermore, claims 5-7 recite myosin and kinesin as part (a) of the recombinant protein, however, claims 5-7 are not so limited to myosin and kinesin as the claims recite analogs, fragments, and derivatives thereof. Thus, the claims encompass a wide variety of proteins with widely variant structures and functions. Thus, there exists substantial variation in both the structures and functions of the claimed recombinant proteins. When there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. This is not the case, and therefore, due to the substantial variation within the genus, the representative number of species as described in the specification is not fairly representative of the entire genus of recombinant proteins.

Claim 28 is drawn to a genus of protein crystals having a crystal lattice formed by a network of proteins of claim 1. The specification teaches only two representative species of protein crystals having a crystal lattice formed by a network of proteins, i.e., M761-2R and M765-DymA2-316 of Table 1 at page 29 of the instant specification. The specification fails to describe any other representative species of

protein crystals by any identifying characteristics or properties other than the functionality of being a protein crystal having a crystal lattice formed by a network of proteins of claim 1. Furthermore, as it appears that applicants intended use of the crystals is for diffraction of X-rays, the specification fails to provide additional representative species of diffraction quality protein crystals. As such, the two representative species of protein crystals disclosed in the specification are insufficient to describe the entire genus of claimed protein crystals. Given this lack of description of representative species encompassed by the genus of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

[9] Claims 1-10, 12, 13, and 28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a recombinant fusion protein comprising a myosin or kinesin protein and a target protein of interest (pertaining to claims 1-10, 12, and 13) and a crystal of the proteins of M761-2R and M765-DymA2-316 in the space group $P2_12_12_1$ (pertaining to claim 28), does not reasonably provide enablement for *all* recombinant proteins as encompassed by claims 1-10 and 13 or a crystal of *all* recombinant proteins as encompassed by claim 28. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Undue experimentation would be required for a skilled artisan to make and/or use the entire scope of claimed recombinant proteins and protein crystals. Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s). The Factors most relevant to this rejection are addressed below.

Regarding claims 1-10, 12, and 13:

- The breadth of the claims: The claims are so broad as to encompass nearly any recombinant protein. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of recombinant proteins broadly encompassed by the claims. In the instant case, the scope of the claims is limited to a recombinant fusion protein comprising a myosin or kinesin protein and a target protein of interest.
- The amount of guidance and working examples: While recombinant proteins and methods of making same are well known to one of skill in the art, the specification fails to provide sufficient enabling guidance for using the entire scope of recombinant proteins. The specification provides fifteen working examples of the claimed recombinant proteins (see Table 1 at page 29 of the instant specification). In all of these examples, it appears that part (a) of the recombinant protein is *Dictyostelium* myosin II fused to various test proteins. Thus, the specification provides guidance in the form of only a single working example of part (a) of the claimed recombinant protein. This guidance and working example is insufficient to enable the entire scope of claimed recombinant proteins. It is noted that while claims 5-7 recite a myosin or kinesin, these claims are not so limited to myosin or kinesin as part (a) of the fusion protein as the claims further recite analogs, fragments, and derivatives thereof. It is unclear from the specification as to how a skilled artisan would use the entire scope of analogs, fragments, and derivatives of the proteins recited in claims 5-7 as the specification has failed to provide guidance for use in this regard.
- The unpredictability and amount of experimentation: There is a high degree of unpredictability associated with the claimed recombinant proteins. For example, from Table 1 at page 29 of the instant specification, it is clear that it is highly unpredictable as to whether the entire scope of claimed recombinant proteins will be expressed by a host cell. Table 1 lists thirteen fusion proteins whose expression was analyzed. Out of the thirteen that were tested, four were not expressed. Thus, nearly one-third of the tested fusion proteins were not expressed. Based on these results a skilled artisan would recognize the high degree of unpredictability in making a desired fusion protein. While most proteins *can* be expressed, one of skill in the art would recognize the large amount of experimentation that would be

required to determine those conditions that allow expression of a desired fusion protein. Also, from the specification, it appears the myosin and kinesin proteins should be functional in order to use the recombinant protein comprising these proteins. However, the specification has provided no guidance as to which of the possible analogs, fragments, and derivatives of myosin or kinesin would be functional and therefore useful.

Regarding claim 28:

- The breadth of the claim: The claim is so broad as to encompass a crystal of any recombinant protein. The claim is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of protein crystals broadly encompassed by the claims. In this case, the scope of the claims is limited to a crystal of the proteins of M761-2R and M765-DymA2-316 produced by the method set forth in paragraph 100 at page 27 of the instant specification.
- The state of the prior art: The prior art indicates that crystallizing proteins is not a routine task. Durbin et al. (*Ann Rev Phys Chem* 47:171-204; IDS reference CE) describe some of the difficulties associated with protein crystallization including the difficulty in purifying proteins to a degree that will allow crystallization, the size and complexity of proteins, and the diversity of chemical groups, which is unique for each protein (page 172, second full paragraph).
- The amount of guidance and working examples: The specification provides insufficient guidance for making and using the entire scope of claimed protein crystals. While methods of crystallizing proteins are known in the art, a skilled artisan would recognize that each protein requires independent considerations when attempts at crystallization are made, particularly for proteins whose crystals are to be used for diffracting X-rays for structural determination. Therefore, a known method for crystallization of a first protein will not necessarily translate to a second protein. The specification provides guidance in the form of only two working examples of protein crystallization – the specific crystals and method for preparing same, which is described at pages 27 and 28 of the instant specification. One of skill in the art would recognize that such guidance is insufficient to enable crystals of the entire scope of claimed recombinant proteins. Also, it appears from the specification that applicants' intended use of the crystals

is for obtaining diffraction data to generate an X-ray crystal structure (see pages 27 and 28 of the instant specification). One of skill in the art recognizes the often extreme difficulty in obtaining diffraction quality crystals. As such, the guidance and working examples provided in the specification are insufficient to enable the entire scope of claimed protein crystals.

- The unpredictability and amount of experimentation: There is a high degree of unpredictability associated with crystallizing proteins. For example, from Table 1 at page 29 of the instant specification, it is clear that it is highly unpredictable as to whether the entire scope of claimed recombinant proteins will crystallize based on the guidance provided in the specification. Table 1 lists four fusion proteins where attempts were made at crystallization. Out of the four that were tested, crystals did not form with two of the recombinant proteins. Thus, half of the tested fusion proteins did not crystallize. Based on these results a skilled artisan would recognize the high degree of unpredictability in crystallizing a desired fusion protein and the large amount of experimentation that would be required to determine those conditions, if any, that allow crystallization of a desired recombinant protein, particularly those conditions for generating diffraction quality crystals.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re* Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re* Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

[10] Claims 1, 2, 5-7, and 13 are rejected under 35 U.S.C. 102(e) as being anticipated by Finer et al. (US Patent 6,410,254). Claim 1 is drawn to a recombinant protein comprising: (a) a first protein, analog, fragment or derivative thereof and (b) a target protein of interest. Claim 2 is drawn to the protein of claim 1 further comprising (c) a linker between (a) and (b). Claim 5 limits (a) of the protein of claim 1 to an amino acid sequence of the myosin or kinesin superfamilies or an analog, fragment or derivative thereof. Claim 6 limits part (a) of the protein of claim 5 to those members of myosin or kinesin superfamilies as recited in the claim or an analog, fragment or derivative thereof. Claim 7 limits part (a) of claim 5 to a motor domain of a member of the myosin or kinesin superfamilies or an analog, fragment or derivative thereof. Claim 13 is drawn to the protein of claim 1 further comprising a tag sequence at the N- or C-terminus. Finer et al. teach fusion proteins comprising a first protein having ATPase activity and a second protein (see columns 17 and 18). Finer et al. teach the first and second proteins can be joined by a peptide linker (column 17, lines 62-64). Finer et al. teach the first protein having ATPase activity can be kinesins and myosins (column 18, lines 36-41) and can be only the ATPase domain (motor domain) of these proteins (column 18, lines 14 and 15). Finer et al. teach the fusion proteins may further include tag polypeptides (column 19, lines 14 and 15). This anticipates claims 1, 2, 5-7, and 13 as written.

[11] Claims 1, 4-7, 9, 10, and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Kurzawa et al. (*Biochemistry* 36 :317-323). Claims 1, 4-7, 9, and 13 are drawn to recombinant proteins as described above. Claim 10 limits part (b) of the protein of claim 9 to those proteins recited in the claim. Kurzawa et al. teach myosin head fragments M754 (amino acids 1-754 *Dictyostelium discoideum* myosin II) or M765 (amino acids 1-765 *Dictyostelium discoideum* myosin II) fused to one (M754-1R or M765-1R) or two alpha-actinin repeats (M765-1R or M765-2R; see page 317, right column, bottom and page 318, left column, bottom). Kurzawa et al. teach the fusion proteins have a histidine octamer at the C-terminus (page 318, right column, top). This anticipates claims 1, 4-7, 9, 10, and 13 as written.

[12] Claims 1, 4-7, 9, 10, and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Manstein et al. (*J Mus Res Cell Mot* 16:325-332 ; IDS reference CF). Claims 1, 4-7, 9, 10, and 13 are drawn to recombinant proteins as described above. Manstein et al. teach a myosin fragment (amino acids 1-754 *Dictyostelium discoideum* myosin) fused to one or two alpha-actinin repeats (see page 326, left column). Manstein et al. teach the fusion proteins have a histidine octamer at the C-terminus (page 326, left column). This anticipates claims 1, 4-7, 9, 10, and 13 as written.

[13] Claim 28 is rejected under 35 U.S.C. 102(b) as being anticipated by Lesburg et al. (*Nat Struc Biol* 6:937-943). Claim 28 is drawn to a protein crystal having a crystal lattice formed by a network of recombinant proteins of claim 1. Lesburg et al. teach the crystallization of a recombinant RNA-dependent RNA polymerase from hepatitis C virus fused to a hexahistidine oligopeptide (page 941, right column, bottom to page 942, left column). This anticipates claim 28 as written.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

[14] Claims 3, 4, and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Finer et al. Claim 3 limits part (c) of the protein of claim 2 to comprising at least 2 amino acids. Claim 4 limits part (b) of the protein of claim 1 to a sequence of at least 20 amino acids. Claim 8 limits (c) of claim 3 to comprising a sequence of 3 amino acids, wherein Gly is in the second position. It is noted that, while claim 8 provides for the limitation of "wherein Gly is in the second position", the use of "comprises a sequence of 3 amino acids" in the claim does not limit the size of the linker and does not limit the position of the glycine residue.

Finer et al. disclose the teachings as stated above. Finer et al. do not specifically teach a linker of at least 2 amino acids having glycine between the two component proteins of their fusion protein.

At the time of the invention, the use of oligopeptide linkers for joining two proteins in a fusion protein was well known to one of ordinary skill in the art. For example, Bulow et al. teaches using peptide linkers and advises using linkers that are short (between two and ten amino acids) as being optimal as longer linkers are often prone to proteolytic cleavage and reduce recombinant protein yields (page 230, left column). Argos teaches the advantages of using oligopeptide linkers comprising Ser, Gly, and Thr as these residues can impart flexibility and maintain stability and conformation in solution (page 956, left column).

Therefore, it would have been obvious to one of ordinary skill in the art for the fusion protein of Finer et al. with a linker of at least 2 amino acids and glycine and a target protein of interest comprising at least 20 amino acids. One would have been motivated for the fusion protein of Finer et al. with a linker peptide comprising at least 2 amino acids and glycine because of the teachings of Bulow et al. and Argos and a target protein of interest of at least 20 amino acids as one of skill in the art would recognize that a large number of proteins that interact with other proteins comprise at least 20 amino acids. One would have a reasonable expectation of success for the fusion protein of Finer et al. with a linker peptide comprising at least 2 amino acids and glycine because of the results of Finer et al., Bulow et al., and Argos and a target protein of interest comprising at least 20 amino acids because of the knowledge of an ordinarily skilled artisan. Therefore, claims 3, 4, and 8, drawn to recombinant proteins as described above would have been obvious to one of ordinary skill in the art.

[15] Claims 2, 3, and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kurzawa et al. (*Biochemistry* 36 :317-323) in view of Bulow et al. (*Trends Biotech* 9:226-231) and Argos (*J Mol Biol* 211:943-958). Claims 2, 3, and 8 are drawn to the recombinant proteins as described above. It is noted that, while claim 8 provides for the limitation of "wherein Gly is in the second position", the use of "comprises a sequence of 3 amino acids" in the claim does not limit the size of the linker and does not limit the position of the glycine residue.

Kurzawa et al. disclose the teachings as stated above. Kurzawa et al. do not teach a linker between their fused protein domains.

At the time of the invention, the use of oligopeptide linkers for joining two proteins in a fusion protein was well known to one of ordinary skill in the art. For example, Bulow et al. teaches using peptide linkers and advises using linkers that are short (between two and ten amino acids) as being optimal as longer linkers are often prone to proteolytic cleavage and reduce recombinant protein yields (page 230, left column). Argos teaches the advantages of using oligopeptide linkers comprising Ser, Gly, and Thr as these residues can impart flexibility and maintain stability and conformation in solution (page 956, left column).

Therefore, it would have been obvious to one of ordinary skill in the art to link M761 and the alpha-actinin repeat(s) using a linker comprising at least two amino acids and glycine. One would have been motivated for the fusion protein of Kurzawa et al. with a linker peptide comprising at least 2 amino acids and glycine because of the teachings of Bulow et al. and Argos. One would have a reasonable expectation of success for the fusion protein of Kurzawa et al. with a linker peptide comprising at least 2 amino acids and glycine because of the results of Kurzawa et al., Bulow et al., and Argos. Therefore, claims 2, 3, and 8, drawn to recombinant proteins as described above would have been obvious to one of ordinary skill in the art.

[16] Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kurzawa et al. (*Biochemistry* 36 :317-323) in view of Van Dijk et al. (*Eur J Biochem* 260:672-683), Ponomarev et al. (*Biochemistry* 39 :4527-4532), Furch et al. (*Biochemistry* 37:6317-6326), and Van Dijk et al. (*Biochemistry* 38:15078-15085). Claim 11 limits (a) of the protein of claim 1 to SEQ ID NO:1.

Kurzawa et al. disclose the teachings as stated above. In addition, Kurzawa et al. teach that "the recombinant nature and the fact that they can be produced and purified in large amounts make M761, M761-1R, and M761-2R ideal constructs for systematic studies of the structure, kinetics, and function of the myosin motor" (underline added for emphasis, page 323). Kurzawa et al. do not teach the sequence of SEQ ID NO:1 (amino acids 1-765 of *D. discoideum* myosin II) as the myosin head fragment.

At the time of the invention, it was well known in the art that M765, a myosin head fragment of amino acids 1-765 of *D. discoideum* myosin II, was useful in the characterization of the structure, kinetics, and function of the myosin motor. Van Dijk et al. (*Eur J Biochem* 260:672-683) teach M765 is the motor domain of *D. discoideum* myosin II and has been shown to retain normal ATP-hydrolysis and actin binding activities (page 672, right column, bottom). Numerous references describe the use of M765 in the structural, kinetic, and functional characterization of the myosin motor – see for example, Van Dijk et al. (*Eur J Biochem* 260:672-683), Ponomarev et al., Furch et al., and Van Dijk et al. (*Biochemistry* 38:15078-15085). Thus, it is clear from the prior art that M765 was useful in the characterization of the structure, kinetics, and function of the myosin motor.

Therefore, it would have been obvious to one of ordinary skill in the art to use amino acids 1-765 of *D. discoideum* myosin II as the myosin head fragment in the fusion protein of Kurzawa et al. One would have been motivated for the fusion protein of Kurzawa et al. with M765 (amino acids 1-765 of *D. discoideum* myosin II) instead of M761 (amino acids 1-761 of *D. discoideum* myosin II) because M765 was well characterized and established for use in the characterization of the structure, kinetics, and function of the myosin motor. One would have a reasonable expectation of success for the fusion protein of Kurzawa et al. with M761 replaced with M765 because of the results of Kurzawa et al., Van Dijk et al. (*Eur J Biochem* 260:672-683), Ponomarev et al., Furch et al., and Van Dijk et al. (*Biochemistry* 38:15078-15085). Therefore, claim 11, drawn to recombinant proteins as described above would have been obvious to one of ordinary skill in the art.

[17] Claims 2, 3, 8, and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Manstein et al. (*J Mus Res Cell Mot* 16:325-332; IDS reference CF) in view of Manstein et al. (*Gene* 162:129-134), and Argos (*J Mol Biol* 211:943-958). Claims 2, 3, and 8 are drawn to the recombinant proteins as described above. Claim 12 limits part (c) of the protein of claim 8 to Leu-Gly-Ser.

Manstein et al. (*J Mus Res Cell Mot* 16:325-332) disclose the teachings as described above. Additionally, Manstein et al. (*J Mus Res Cell Mot* 16:325-332) teach that the plasmid used for expression of their fusion protein was derived from plasmid pDXA-3H (page 326, left column). Manstein et al. (*J Mus*

Res Cell Mot 16:325-332) do not teach the presence of a Leu-Gly-Ser linker linking the myosin and alpha-actinin component proteins of their fusion.

Mainstein et al. (*Gene* 162:129-134) teach an expression vector, pDXA-3H, with two restriction sites, KpnI and SacI, followed by nucleotides encoding Leu-Gly-Ser followed by XhoI and NsiI restriction sites.

Argos discloses the advantages of using a linker comprising Gly, Ser, and Thr as described above.

Also, at the time of the invention, the use of inserting nucleic acids encoding a particular protein into an expression vector using a known restriction site present in the expression vector were well known in the art. The restrictions sites KpnI, SacI, XhoI, and NsiI were well known restriction sites commonly used for insertion of nucleic acids into an expression vector at the time of the invention.

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Manstein et al. (*J Mus Res Cell Mot* 16:325-332) and Manstein et al. (*Gene* 162:129-134) for constructing an expression vector by inserting a nucleic acid encoding M754 into either the KpnI or SacI restriction sites of pDXA-3H and inserting a nucleic acid encoding the alpha actinin repeat(s) into the XhoI and NsiI restriction sites of pDXA-3H to generate the fusion protein of Manstein et al. (*J Mus Res Cell Mot* 16:325-332) with a linker comprising Leu-Gly-Ser. One would have been motivated to construct an expression vector by inserting a nucleic acid encoding M754 into either the KpnI or SacI restriction sites of pDXA-3H and inserting a nucleic acid encoding the alpha actinin repeat(s) into the XhoI and NsiI restriction sites of pDXA-3H to generate the fusion protein of Manstein et al. (*J Mus Res Cell Mot* 16:325-332) with a linker comprising Leu-Gly-Ser in order to exploit the presence of restriction sites within vector pDXA-3H and to have a fusion protein with a linker comprising Gly and Ser as taught by Argos. One would have a reasonable expectation of success for constructing an expression vector by inserting a nucleic acid encoding M754 into either the KpnI or SacI restriction sites of pDXA-3H and inserting a nucleic acid encoding the alpha actinin repeat(s) into the XhoI and NsiI restriction sites of pDXA-3H to generate the fusion protein of Manstein et al. (*J Mus Res Cell Mot* 16:325-332) with a linker comprising Leu-Gly-Ser because of the results of Manstein et al. (*J Mus Res Cell Mot* 16:325-332) and Manstein et al.

(*Gene* 162:129-134). Therefore, claims 2, 3, 8, and 12, drawn to recombinant proteins as described above would have been obvious to one of ordinary skill in the art.

Conclusion

[18] All claims are rejected. No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Thursday from 6:30 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for official papers filed to Group 1600 is (703) 308-4242. Draft or informal FAX communications should be directed to (703) 746-5078. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.
Patent Examiner
Art Unit 1652

PONNATHAPURA ACHUTAMURTHY
SUPERVISORY PATENT EXAMINER
TELEPHONE NUMBER 1303